SIMPSON WOOLLEY
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May 6, 2005

VIA FEDERAL EXPRESS

Food and Drug Administration
Department of Health and Human Services
Division of Dockets Management Branch
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Citizen Petition of Terry Fredeking and Antibody Systems, Inc.

Gentlepeople:

Enclosed please find an original and three (3) copies of the Citizen Petition of Terry Fredeking and Antibody Systems, Inc. in the above referenced matter. Please file the original and return the file marked copies in the return envelope.

Thank you in advance for your anticipated cooperation. If you have any questions regarding this matter, please feel free to contact me.

Sincerely,

Charles R. McConachie
CRM/qlc
Enclosure
cc: Client (w/encl.)

2005P-0182

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ORIGINAL

US FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF DOCKETS MANAGEMENT

CITIZEN PETITION OF	§	**NO.**_____
	§	
TERRY FREDEKING AND	§	
	§	**MAY 6, 2005**
ANTIBODY SYSTEMS, INC.	§	

CITIZEN PETITION

The undersigned submits this petition pursuant to 21 CFR 10.30, Chapter 4 of the Regulatory Procedures Manual and 21 USC 701 of the Food Drug and Cosmetic Act (Act), the Freedom of Information Act, 5 USC 552 et seq. (FOIA) and relevant regulations for which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR 5.10 to petition the Commissioner of Food and Drugs (Commissioner) to take the following requested final agency administrative action.

A. Action Requested

This Citizen Petition involves the April 14, 2003, Warning Letter sent by the Center for Biologics Evaluation and Research (CBER) following a December 16-17, 2002, inspection of the North Texas Institutional Review Board (NTIRB), the issuance of a FD-483 to the NTIRB and the subsequent written NTIRB response. Instead of sending the Warning Letter to the NTIRB, CBER, incorrectly, sent the Warning Letter to Terry Fredeking, President, Antibody Systems, Inc. This action was against the procedures, practices, and regulations of the Agency, was a denial

of due process and was unlawful. The failure of CBER to correct the improper action as requested by the Petitioners is also a denial of due process and against the policy, regulations and practice of FDA.

The specific action requested is for the Commissioner to (1) withdraw in its entirety the April 14, 2003, Warning Letter, CBER 03-010, addressed to Terry Fredeking, President, Antibody Systems, Inc. (ASI), from the Warning Letters Web Page of FDA and in response to FOIA requests for such Warning Letter, and if deemed appropriate by the agency the reissuance of the Warning Letter to NTIRB, or (2) the redaction from the warning letter displayed on the Warning Letters Web Page of FDA and in response to FOIA requests of "Terry Fredeking" and "ASI" in the form set out in Exhibit 1 to this Citizen's Petition, or (3) publish on the Warning Letters Web page and in response to any FOIA requests the response of ASI and Mr. Fredeking to the April 14, 2003, Warning Letter in the form set out in Exhibit 2 to this Citizen's Petition.

B. Statement of Grounds

1. Facts

In 1991 NTIRB began operations at 605 S. West Street, Arlington, Texas. Due in large part to a lack of demand for its services, the IRB ceased all operations in 2000, only holding files on the trials until 2003. The chairman of the NTIRB, DR. Neil Dishon, MD, resigned his position on or about January 3, 2001. The announced inspection by FDA occurred on December 16-17, 2002.

During the years it was in operation, NTIRB had seven members whose make up changed from time to time. The chairman, Dr. Dishon, served as chairman of NTIRB at all relevant times. The IRB members were Registered Nurses, an ordained minister, a lay pubic member and several professors/scientists on the faculty of The University of Texas at Arlington (UTA). Dr. Dishon was employed at UTA as the chief physician of student health services. While, NTIRB was not an official IRB of UTA, its scientific members were all on the faculty of UTA and there were strong ties to UTA. NTIRB was at all times ready and available to serve as an IRB for clinical trials of drugs and devices. Between 1991 and 1999, NTIRB approved and reviewed 13 different studies. As shown in Exhibit 3 the studies came from a number of different sponsors. The studies from other sponsors were presented to the IRB by ASI, located in Hurst, Texas. Because of a lack of activity the NTIRB ceased undertaking any studies in 1999, ceased operations in 2000, and gave notice to sponsors concerning the return of study documents in 2003.

In December 2002, NTIRB was inspected by FDA. This announced inspection was the first one for NTIRB under Compliance Program 7439.809. The inspectors were advised that NTIRB had disbanded in 1999, but that Dr. Dishon ". . . was the most responsible person to represent the IRB in the inspection, since he had been chairman for the entire period the IRB was active." See page 2 of the NTIRB EIR, a copy of which is attached as Exhibit 4. The Notice of Inspection

(FD-482) was presented to Dr. Dishon on December 16, 2002 even though FDA knew the IRB had not been active for several years. On December 17, 2002, the investigators presented the FD-483 to Dr. Dishon, as former chairman. See Exhibit 5, attached.

During the inspection the investigators observed a number of purported deficiencies regarding the operation of the IRB in record keeping, procedures being written, continuing reviews of trial research, retention of records and documents, inadequate records of reviews of proposed protocols, possible conflicts of interest, lack of records with the IRB, and the statement that the trials conducted under NTIRB's umbrella were all by ASI.

Following the presentation of the FD-483 on December 17, 2002, to Dr. Dishon, chairman of the NTIRB, the NTIRB sent FDA its written response, on or about January 22, 2003. The thrust of the response, a copy of which is attached as Exhibit 6, was to reply to each of the FD-483 observations, to assure FDA that the two studies approved in 1999 (the last approvals) were a one-day study that was exempt from IND requirements and another study the sponsor canceled before it was conducted, and to assure FDA that if for some reason NTIRB were to be reactivated, "substantial and definitive action would be taken to comprehensively address each of the observations to ensure that the IRB operates in full compliance with all applicable obligations." Id., page 1.

On April 14, 2003, FDA sent a Warning Letter regarding the December

2002, inspection of NTIRB not to Dr. Dishon, but to Terry Fredeking, President of ASI. See Exhibit 7, attached. While acknowledging that Dr. Dishon was identified by the inspectors as the most responsible person at NTIRB when the FD-483 was presented, the Warning Letter goes on to state that "[t]his letter is addressed to you because the IRB was established to review only studies sponsored by, or conducted under contracts to, Antibody Systems, Inc." Additionally, the Warning Letter went on to state ". . . you appear to be the most responsible party regarding the operations of this IRB. The FDA investigators met with you during part of the inspection."[1]

On May 7, 2003, a written response to the Warning Letter was submitted to FDA. See Exhibit 8. The response addressed each of the areas of the Warning Letter relating to how the IRB had operated in the various trials. Additionally, the response confirmed what Dr. Dishon said in the response to the FD-483, that NTIRB had not be active for some years, and that the IRB was still in existence only to wind up its affairs and to keep necessary records.

- Dr. Dishon stated that "if an IRB were to be reconstituted, substantial and definitive action would be taken to comprehensively address each of the observations to ensure the IRB operates in full compliance with all applicable regulations."

- Mr. Fredeking stated that ASI would not use the services of NTIRB again, would use a professional full time IRB, and had removed any reference on its web page to NTIRB.

- Finally, Mr. Fredeking stated ASI had done nothing more than provide secretarial and similar administrative support requested by

1 A reading of the EIR involving responsibility does not bear this statement out.

Dr. Dishon.[2]

The next communication from FDA was an August 25, 2003, letter from the District Director of FDA transmitting a copy of the Establishment Inspection Report (EIR) of the IRB to Dr. Dishon of the NTIRB. See Exhibit 9, attached. Neither API nor Mr. Fredeking were sent a copy.

An EIR is the most single detailed report of an inspection that is created by FDA. It is the document that senior FDA officials review when making decisions about what enforcement action, if any, to undertake or recommend. The reason for the EIR's statements being given this deference by FDA is the investigators were present at the inspection and personally witnessed what they list as observations of non-compliance of law and regulation.

In the inspection of NTIRB, the investigators did not identify Mr. Fredeking as the most responsible person in issuing the FD-482 or in the FD-483. The only person listed as having individual responsibilities was Dr. Dishon. At page 3 of the EIR,

> "Dr. Dishon stated that, although he has resigned as Chairman of the IRB, he is the most responsible person and had knowledge of all of the previous activities of the board. He said that, at present, there is no IRB Chairman. All correspondence should be directed to him at: . . . "

Throughout the EIR the conversations between the FDA investigators and Dr.

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[2] This is consistent with the EIR in which the investigators noted at page 4 that ASI "handled most of the administrative details of the IRB, including maintaining meeting minutes, writing approval letters for Dr. Dishon's signature, scheduling IRB meetings and distributing study-related materials to IRB members."

Dishon are reported. In Observation No. 7 on the FD-483, repeated in the EIR, it was reported that one IRB member, Dr. George Stewart, had voted on the proposed studies of API while an employee of API. This is an incorrect statement as has previously been pointed out to FDA[3]. The investigators never interviewed Dr. Stewart or ASI. The statement is based solely on a CV of Dr. Stewart, which does not say he was an employee of ASI. In fact, Dr. Stewart was at all times a full-time employee of UTA. Dr. Stewart is a PhD., specializing in the study of parasites. ASI did conduct certain research in the laboratory of Dr. Stewart at UTA concerning parasites over a period of time. None of the studies voted upon by the IRB involved parasites.

While Dr. Stewart did consult with ASI in parasitology and did receive a small honorarium for the use of the laboratory, ASI never sought to influence Dr. Stewart. Attached as Exhibit 10 is the affidavit of Dr. Stewart stating that his employer at all relevant times was UTA, his role on NTIRB, the nature of any relationship with ASI, the fact that his vote was his vote, and that the IRB discontinued operations five years ago.

Dr. Dishon never confirmed that Dr. Stewart was an ASI employee. There is

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[3] Dr. Dishon's response to the FD-483 on this point at page 5 stated that

"Dr. Stewart was not an employee of Antibody Systems. He was a full-time employee of the University of Texas, who also was a consultant to Antibody Systems. In his consulting role he carried out *non-clinical* research activities at his lab[ratory] at the university for Antibody Systems that was entirely unrelated to the products involved in the clinical protocols. . . . He never had any role in the conduct or supervision of the clinical studies or a financial interest in their performance or outcome. Accordingly, the IRB did not believe he had a disqualifying conflict of interest . . [H]is vote did not change the outcome of any decision taken by the IRB."

nothing in the record to suggest the investigators even asked one way or the other. Finally, there is nothing in the EIR to suggest that any vote of Dr. Stewart was outcome determinative of any proposed study.[4] The only statement on this point is the Affidavit of Dr. Stewart in which he states his vote was his.

Sometime after the April 16, 2003, Warning Letter was sent a copy of the Warning Letter was posted on FDA's Web Page under "Warning Letters." See Exhibit 11, attached.

On December 29, 2003, Mr. Fredeking wrote FDA about the posting of the Warning Letter on FDA's Web Page and the fact that the Warning Letter was incorrect. See Exhibit 12, attached. Mr. Fredeking requested that FDA redact the names of ASI and Fredeking from the Warning Letter on the grounds that it was factually incorrect and contrary to proper FDA practices for the issuance of Warning Letters.

Almost eight months later by letter dated August 26, 2004, CBER's Office of Communication, Training and Manufacturers Assistance denied Mr. Fredeking's request on the ground that ASI was the "institution" responsible for NTIRB, because NTIRB had no chairman at the time of the inspection and because the inspection showed that Mr. Fredeking "played a significant role" in the operations

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[4] At page 26 of the EIR the investigators advised Dr. Dishon that it appeared that ASI had been closely involved with the IRB. Dr. Dishon agreed that ASI had created the IRB to have an IRB to review studies and that ASI did provide administrative support for the IRB as there was no one in Dr. Dishon's UTA office to do so. However, it is clear that ASI at no time either controlled the NTIRB or that its activities were a rubber-stamp of ASI. See the affidavits of Dr. Dishon , Romalee Harris, RN, DC, and Patricia Okimi, Phd, attached as Exhibit 16 , Exhibit 17 , Exhibit 18, and Joel Montgomery, Ph.D., M.Sc., Exhibit 19, respectively. See also the affidavit of Dr. Stewart, attached as Exhibit 10.

of NTIRB. See Exhibit 13, attached.

On September 15, 2004 ASI replied to the letter of August 26, 2004, see Exhibit 14. In the September 16th letter Mr. Fredeking pointed out that the Warning Letter ". . . should not have been directed to either our firm or me personally." The reasons for this statement were

- The December 16-17, 2002 prearranged inspection took place at the office of the NTIRB, in Arlington, Texas.
- The FD-482 was issued to Dr. Neil Dishon, MD, NTIRB chairman at all relevant times.
- The FD-483 was presented to Dr. Dishon, as the responsible person. He stated that all correspondence should be sent to him.
- Dr. Dishon responded to the FD 483 in writing and fully responded to each item on theFD-483.
- The EIR at page 3 provides under "Persons Interviewed and Individual Responsibilities" that Dr. Dishon "is the most responsible person and has knowledge of all the previous activities of the board."
- There is no record of any interview of Mr. Fredeking in the section of the EIR where interviews are reported.
- No FD-482 or FD-483 was issued or presented to Mr. Fredeking.
- Sending the Warning Letter to Mr. Fredeking without any prior notice was a denial of due process under FDA practice, guidance and regulations.

Finally, on October 5, 2004 the Acting Director of CBER Office of Compliance advised Mr. Fredeking that his request of September 15, 2004 to have that response posted on the FDA Web Site as a response to the April 14, 2003 Warning Letter addressed to the NTIRB was denied because the response would ". . . likely mislead the public concerning the facts pertinent to the matter. . . " because that letter does not address the issues of the Warning Letter. Exhibit 15.

Having unsuccessfully sought relief from CBER under the Act and FOIA,

this Citizen's Petition is presented for final agency action and for justice to be done.

2. Argument

The Warning Letter issued by CBER in this instance did not comply with FDA policy. Chapter 4-1-10 of the Regulatory Affairs Manual provides in pertinent part that a "Warning Letter" . . . is

> "3. Issued to the responsible individual who, based upon currently available evidence, is most closely related to the violation, to that person's superior, and to the highest known official . . . in the organization."

The justification by CBER for issuing the Warning Letter to Mr. Fredeking was that an ASI employee was a voting member of the IRB; ASI controlled the IRB, and accordingly was the parent. Contrary these conclusions in the August 26, 2003, letter it is clear that CBER is wrong and the Warning Letter should never have been sent to Mr. Fredeking. For example, the CBER statement that an ASI employee was a voting member of the IRB is simply not true. Despite NTIRB's pointing this fact out in its response to the FD-483, sometime after the EIR was prepared CBER decided to send a Warning Letter not to Dr. Dishon, the person who by his own statement was the most responsible person for the IRB, but to Mr. Fredeking. This improper and inappropriate action is the basis of this Citizen's Petition. Because such information is unilaterally made public by FDA and posted on its. Web Page the submission of this Citizen's Petition is necessary to have FDA act in compliance with its own law, regulation and guidance.

The dividing line between a sponsor, researcher and IRB that CBER portrays in this case as improper is not substantiated by FDA's own 2001 Draft Guidance regarding relationships in clinical research issues between IRBs researchers and sponsors. As stated in the Draft Guidance at page 1, ". . . there is currently no uniform, comprehensive approach to consideration of potential financial conflict of interest in human research."

The Draft Guidance goes on to say that

> "[r]ecognizing that practices and procedures are evolving in this area in the private sector and that there are as yet no 'best practices' and that there is little consensus on what is 'right' and what is 'wrong' at this time, HHS is offering this guidance to assist . . . IRBs in their deliberations concerning potential and real conflicts of interest. . . ." Id.

The NTIRB was formed in 1991. The Draft Guideline quoted above was published in 2001, well after the NTIRB ceased operations. CBER has completely ignored the fact that its 2003 Warning Letter concerns alleged events that took place going back to 1991 and that by 2001 when FDA published the Guideline saying there was "no uniform, comprehensive approach" the NTIRB had not conducted any business for several years. We submit it is wrong to apply in 2003 standards that were not determined with finality in 2001 and almost virtually non-existent in 1991.

As recently as March, 2005, the Associated Press reported that six expert members of US funded AIDS study Panel had received grants between $120,000 to $2,000,000 a year from the National Institutes of Health, the governmental

agency which is the subject of the probe. The financial payments were known to the Institute of Medicine, but they were approved by the Institute because there was no conflict of interest. While perhaps not directly on point, the Associated Press article does demonstrate that even in 2005 the government has no consistent uniform standard regarding research, researchers, and money. That being the case, CBER's actions here are even more indefensible. If a $2,000,000 grant per year to a member of a significant AIDA panel is acceptable, as reported by the AP, how can the Warning Letter here be justified on the grounds of possible conflict of interest?

Further support for the conclusion that the Warning Letter here was improperly sent comes from FDA's Regulatory Procedures Manual on Warning Letters.

Under definitions, a Warning Letter

> . . is a correspondence that notifies regulated industry about violations that FDA has documented during its inspections and investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected."

First, sending a Warning Letter in this instance did not follow FDA's own regulatory procedures. The policy is clear: a Warning Letter "should" be issued **only** where an enforcement action will follow unless the violations are not

corrected. In the case of NTIRB while the investigators made a number of observations echoed in the Warning Letter, the IRB had ceased virtually all activities long before the inspection of December 2002. As a result, under the FDA's own regulatory procedures no Warning Letter was appropriate. With the IRB having ceased activities long before the inspection and with the inspectors knowing the IRB was not going to be constituted, there was nothing of substance for the IRB to do to promptly and adequately correct the observations listed with an eye towards making the next clinical trial submitted comply with FDA law and regulation.

A review of the list of observations carried forward to the Warning Letter shows that in the main the deficiencies were over what had happened well in the past during one or more of the studies and/or over problems in producing documents promptly when asked. The response of the IRB to the FD-483 showed this theme--

- No.1 "Due to the long period since the IRB ceased activity we have not located all of the procedures used. . . We agree . . . that copies of specific written procedures used should have been available for review."

- No. 2 "The studies . . . were completed more than three years ago before the inspection and thus most of the records are no longer available. . . . No studies are now under IRB review and none will be undertaken. . . ."

- No 3. "Because these studies are past the required record retention period it is not possible to obtain the documents indicated. . . "

- No.4. No records in three of four studies as they were completed

more than three years ago. ". . . [N]o research under the protocol was performed after the last subject was enrolled in October 1999 and the notice of termination received on July 10, 2000. Thus there would be no progress reports." The IRB did locate the consent form and study documents for the fourth study and so advised FDA.

- No. 5. Again, the observation involves three studies completed more than three years earlier and one in which the IRB did locate some of the documentation requested. Again, the IRB pointed out that ". . . [N]o research was in fact conducted under the approval of that meeting.

- No 6. Again, the observation involved three studies completed more than three years before the inspection and the fourth, ". . . a minimal risk study, properly conducted under expedited review. . ."

- No. 7. The observation that a voting IRB member had a conflict, as he was an employee of the sponsor of the studies the IRB reviewed was pointed out to be wrong in the FD-483 response. No one ever looked beyond the CV of Dr. Stewart.

The observations would not under the FDA regulatory procedures serve as a sound foundation for sending a Warning Letter to the NTIRB and especially to Mr. Fredeking.

Sending a Warning Letter following a FDA inspection may further the interests of the agency, but not be justified by FDA practice or guidance, the Food Drug and Cosmetic Act and the FOIA.

In Section 4.1 of FDA's Regulatory Procedures Manual quoted from above, the following is included under the definition of Warning Letter.

> "A Warning Letter . . . is a correspondence that notifies **regulated industry about violations that FDA has documented during inspections or investigations.**" (emphasis added).

Since one admitted intent of FDA for issuing a Warning Letter, besides of

putting the addressee on personal notice of the perceived problem(s), is to notify regulated industry of violations, it is obvious that great care should be used to make sure the Warning Letter is (1) appropriate and (2) is addressed to the correct individual. A Warning Letter is appropriate when violations of "regulatory significance" need to be corrected promptly and adequately. The correct person to whom to address the Warning Letter is the "responsible individual."

By including "notifies" [the] regulated industry" as part of the definition of a Warning Letter FDA purposefully discloses on its Web Page each Warning Letter sent. Such disclosure is neither authorized by the Act or FOIA. What the procedure does for FDA is surround the addressee with a "target" sign and lets everyone in the industry know not only what violations of FDA law the Agency is sending Warning Letters out over, but who is receiving the letters.

At this time this Petition does not challenge the per se release of all Warning Letters on the FDA Web Page, although the legality of the practice is open to question. Because of publishing all Warning Letters FDA's Web Page results in such serious and potentially severe ramifications, it does mean that FDA must be cognizant of its own power and follow its regulatory procedures at all times.

The Warning Letter issued here was not justified under FDA's own regulatory procedures. Neither was sending the Warning Letter to the wrong individual justified under FDA's regulatory procedures.

The responsible person as set out in the Act and in case law was properly

identified by the investigators as the head of the IRB, Dr. Dishon. The affidavits of certain IRB members establish that Mr. Fredeking did not play any substantive role in the decisions of the IRB. He did not vote. Employees of ASI company were not members of the IRB,[5] and did not determine the outcome of any action of the IRB.

For FDA to have sent the Warning Letter to Mr. Fredeking and publish it on FDA's Web Page was administrative error the Center has to date refused to acknowledge. For that reason this Petition is necessary and should be granted for the reasons stated above.

C.

Environmental Impact

The Petitioner claims categorical exclusion under 21 CFR 25.30 et. seq. No environmental assessment is necessary.

D.

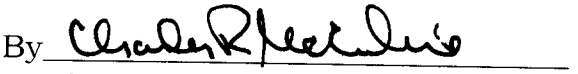
Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner, which are unfavorable to the Petition.

[5] Mr. Fredeking was under 21 CFR 56.107(f) a nonvoting participant in the IRB in an administrative support role.

Respectfully Submitted,

Simpson Woolley McConachie, LLP

By 

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May 11, 2005

Via Facsimile 301 927 6830

Lyle Jaffe
Food and Drug Administration
Department of Health and Human Services
Division of Dockets Management Branch
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Citizen Petition of Terry Fredeking and Antibody Systems, Inc.

Dear Mr. Jaffe:

This will confirm our telephone conversation earlier today to the effect that we do not object to two of the exhibits attached to our Citizen's Petition, Exhibit Numbers 6 and 8, from being disclosed.

The Exhibit Numbers contain the term, "confidential", but for this Citizen Petition they are not.

Please call me if you have any further questions.

Sincerely,

Charles R. McConachie

CRM/qlc
cc: Antibody Systems, Inc.